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(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

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5 August 1999 (05.08.99)

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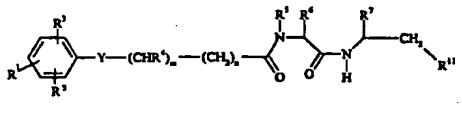

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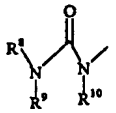

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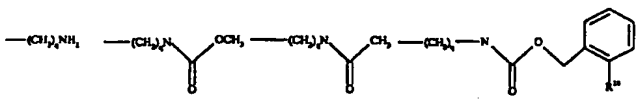

(B)

(57) Abstract

Compounds of formula (II) where R^1 is in the para or meta position and is (A); R^2 and R^3 are each independently selected from hydrogen, nitro, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyl, C_{1-6}alkylamino, C_{1-6}dialkylamino, C_{1-6}alkylC_{1-4}alkoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, amino, cyano, halogeno, trifluoromethyl, $-CO_2R^{12}$ and $-CONR^{12}R^{13}$, where R^{12} and R^{13} are independently selected from hydrogen or C_{1-6}alkyl, or R^2 and R^3 together with the phenyl to which they are attached form a 9 or 10 membered bicyclic ring system; R^4 is C_{1-4}alkyl; R^5 is selected from hydrogen and C_{1-4}alkyl; R^6 is selected from C_{1-6}alkyl, C_{1-4}alkyl(C_{4-6})cycloalkyl, C_{1-6}alkyl(C_{1-6})alkoxyl, C_{1-6}alkylS(C_{1-6})alkyl, C_{1-4}alkylsulphonyl(C_{1-4})alkyl; (B) where q is an integer from 1 to 6 and R^{14} is halogeno; R^7 is selected from C_{1-6}alkyl, C_{1-8}alkoxylcarbonyl, C_{2-6}alkenyl, 1,3–benzodioxol–5–yl and aryl each optionally substituted by one or more substituents selected from C_{1-4}alkoxy, C_{1-6}alkyl, cyano, halogeno, and trifluoromethyl; R^8 is aryl, heteroaryl, a bicyclic heteroaryl ring system linked to the nitrogen via a ring carbon or a 9 or 10 membered bicyclic ring system linked to the nitrogen via a ring carbon and each ring is optionally substituted with up to two substituents, which may be the same or different, and are selected from C_{1-6}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-6}alkylC_{1-4}alkoxyl, C_{1-6}alkylaminoC_{1-6}alkyl, hydroxy, $-CO_2H$, $-(CH_2)_pOH$ where p is 1 or 2, cyano, halogeno, and trifluoromethyl; R^9 and R^{10} are each independently selected from hydrogen and C_{1-4}alkyl or R^8 and R^9 together with the nitrogen to which they are attached form a dihydroindolyl, or a dihidroquinolinyl group; R^{11} is selected from carboxyl, tetrazolyl, alkyl sulphonylcarbamyl, sulfo and sulfino; Y is oxygen, sulphur or sulfonyl; m is 0 or 1; and n is 0 or an integer from 1 to 4 with the proviso that when m and n cannot both be 0 and when m is 1, n is 0; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof. The compounds inhibit the interaction of vascular cell–adhesion molecule–1 and fibronectin with integrin very late antigen 4 ($\alpha_4\beta_1$). They have therapeutic applications such as in multiple sclerosis, rheumatoid arthritis, asthma, coronary artery disease and psoriasis.

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 98/03334

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C275/34 C07D317/60 C07C317/50 C07D405/12 C07D407/12
C07D409/12 C07D417/12 C07D413/12 C07C323/60 C07K5/02
A61K31/195 A61K31/36 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 22966 A (BIOGEN INC) 1 August 1996 cited in the application see table 1; claims 1, 28-33	1,6,8-10
A	WO 97 08145 A (G.D. SEARLE & CO) 6 March 1997 see page 4, line 18 - page 13, line 6; examples 108, 124	1,6,8-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 May 1999	21/05/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03334

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 8-9
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 8-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Intern ıal Application No
PCT/GB 98/03334

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9622966 A	01-08-1996	AU 4911596 A	14-08-1996
		BG 101841 A	30-04-1998
		BR 9606778 A	06-01-1998
		CA 2211181 A	01-08-1996
		CN 1177343 A	25-03-1998
		CZ 9702340 A	18-03-1998
		EP 0805796 A	12-11-1997
		FI 973087 A	22-09-1997
		HU 9702461 A	28-04-1998
		JP 10513160 T	15-12-1998
		NO 973384 A	19-09-1997
		PL 321848 A	22-12-1997
		SK 98797 A	04-02-1998
WO 9708145 A	06-03-1997	AU 702487 B	25-02-1999
		AU 7103996 A	19-03-1997
		CA 2230209 A	06-03-1997
		CN 1201454 A	09-12-1998
		CZ 9800341 A	16-09-1998
		EP 0850221 A	01-07-1998
		NO 980817 A	24-04-1998
		NZ 318926 A	29-04-1999
		PL 325312 A	20-07-1998